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(12) PATENT ABRIDGMENT (11) Document No. AU-B-49148/93
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 668767

(54) Title
ORAL MEDICAMENT FORM

International Patent Classification(s)
(51)^5 A61K 009/28

(21) Application No. : 49148/93 (22) Application Date : 20.10.93

(30) Priority Data

(31) Number	(32) Date	(33) Country
4236025	24.10.92	DE GERMANY

(43) Publication Date : 05.05.94

(44) Publication Date of Accepted Application : 16.05.96

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(56) Prior Art Documents
JP 61-129138

(57) Claim

1. Oral medicament form comprising at least one active compound and at least one enveloping material which surrounds the active compound and comprises at least one film-forming agent which is insoluble in water and the digestive juices, characterized in that the enveloping material additionally comprises at least one cyclodextrin and/or at least one of its derivatives.

2. Enveloping material for oral medicament forms, comprising at least one film-forming agent which is insoluble in water and the digestive juices, characterized in that it additionally comprises at least one cyclodextrin and/or at least one of its derivatives.

Our Ref: 482543

668767

P/00/011
Regulation 3:2

AUSTRALIA

Patents Act 1990

ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

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Invention Title: Oral medicament form

The following statement is a full description of this invention, including the best method of performing it known to me:-

5020

Oral medicament form

The invention relates to a new oral medicament form comprising at least one active compound and at least one enveloping material which encloses the active compound and comprises at least one film-forming agent which is insoluble in water and the digestive juices, characterized in that the enveloping material additionally comprises at least one cyclodextrin and/or at least one of its derivatives.

The invention furthermore relates to an enveloping material for oral medicament forms, comprising at least one film-forming agent which is insoluble in water and the digestive juices, characterized in that it additionally comprises at least one cyclodextrin and/or at least one of its derivatives.

The invention was based on the object of providing oral medicament forms in which the active compounds are released in the colon in a controlled manner. Such medicament forms are known per se.

As a rule, they comprise a coating which is resistant in the stomach and small intestine and is first broken down in the colon and thereby allows release of the active compound. EP 0 485 840 A2 thus describes a coating agent which comprises a polysaccharide which can be broken down in the colon and, mixed therewith, a film-forming polymer material. Coating agents of this kind, however, still have certain disadvantages. For instance, they are hard, and the active compounds are not always released specifically in the colon.

DE 41 31 292 A1 describes galactomannan derivatives for encasing or embedding medicament active compounds. These galactomannan derivatives are new substances, the toxicological acceptability of which has not yet been demonstrated to date.

In other cases, for example in the case of microcapsules and semipermeable casings, for example ethylcellulose, the release is subject to wide individual variations.

These disadvantages of the known medicament forms are avoided or at least reduced by the oral medicament form described above.

Suitable medicament forms are, in particular, tablets, coated tablets, sachets, capsules, pellets, sprinkling beads, granules, crystals or powders. The medicament form can also be in an embedding material which comprises at least one active compound embedded, together with at least one cyclodextrin, in a film-forming agent which is insoluble in the digestive juices.

Preferred suitable film-forming agents are, according to the invention, polyacrylates, polymethacrylates and copolymers thereof and also ethylcelluloses, in particular highly substituted ethylcelluloses. Commercially available dispersions which comprise copolymers of acrylic and methacrylic acid esters and have a low content of quaternary ammonium groups, the molar ratio of these ammonium groups to the other neutral (meth)acrylic acid esters being between about 1:10 and 1:50, preferably 1:20 and 1:40, and the average molecular weight being about 150,000, are particularly advantageously used.

The cyclodextrins used according to the invention are α-glycosidically linked oligosaccharides, in contrast to the β-glycosidically linked polysaccharides used according to EP 0 485 840 A2.

The preferred cyclodextrin is β-cyclodextrin ("CD"; seven glucose units). However, α-cyclodextrin (six glucose units) and γ-cyclodextrin (eight glucose units) are also suitable. Possible derivatives of the cyclodextrins are hydroxypropyl-CD, hydroxyethyl-CD and poly-CD.

The enveloping material according to the invention can comprise further auxiliaries and/or additives. The addition of plasticizers is thus advantageous.

Particularly preferred suitable plasticizers are alkyl esters of di- or tricarboxylic acids, such as diethyl phthalate ("DEP") or triethyl citrate ("TEC"). As can be seen under a polarization microscope, CD is present in the TEC-containing materials in essentially unchanged form; in contrast, in the case of the DEP-containing materials, a crystalline structure is detectable. Other suitable plasticizers are, for example, (other) citric and tartaric acid esters (acetyltriethyl, acetyltributyl and tributyl citrate); glycerol and glycerol esters (glycerol diacetate and triacetate, acetylated monoglycerides and castor oil); phthalic acid esters (dibutyl, diamyl, dimethyl, dipropyl and di-(2-methoxy or -ethoxyethyl) phthalate and ethylphthalyl- and butyl-phthalylethyl and -butyl glycolate); alcohols (propylene glycol and polyethylene glycol of different chain lengths); adipates (diethyl and di-(2-methoxy- or -ethoxyethyl) adipate); benzophenone; diethyl and dibutyl sebacate, succinate and tartrate; diethylene glycol dipropionate; ethylene glycol diacetate, dibutyrate and dipropionate; tributyl phosphate and tributyrin; polyethylene glycol sorbitan monooleate; sorbitan monooleate; and polyethylene oxide/polypropylene oxide block polymers.

The addition of small amounts of water-soluble substances such as polyethylene glycols, polyvinylpyrrolidone, a copolymer of polyvinylpyrrolidone and polyvinyl acetate, hydroxypropylcellulose and hydroxypropylmethylcellulose furthermore is possible. Solids such as talc and/or magnesium stearate and dyestuffs and pigments can also be added to the enveloping material. Furthermore, addition of lipophilic substances, such as, for example, 20-30% stearic acid, can reduce the permeability of the films to water vapour and thus improve the storage life of substances which are sensitive to moisture.

If appropriate, an insulating layer can be applied between the core and auxiliary material and can comprise, for example, hydroxypropylcellulose, hydroxy-

propylmethylcellulose or polyvinylpyrrolidone.

A final protective lacquer can also be used. Substances which are suitable for this purpose are, for example, cellulose acetophthalate, hydroxypropylmethylcellulose phthalate, polyvinyl acetophthalate, shellac, hydroxypropylmethylcellulose acetosuccinate, carboxymethylcellulose, cellulose acetotrimellitate and copolymers of maleic acid derivatives and phthalic acid derivatives.

The enveloping material expediently comprises 30-90%, preferably 40-75%, of film-forming agent, 0-30%, preferably 8-15%, of plasticizer and 10-70, preferably 12-50% of cyclodextrin.

The encasing of the active compounds or the pharmaceutical formulations, that is to say the formulations into which the active compounds are incorporated together with the customary or necessary pharmaceutical auxiliaries, is carried out by methods known in pharmaceutical technology, or the customary processes for coating medicament forms.

Therapeutic active compounds are likewise embedded by methods known in pharmaceutical technology. Instead of the plastic or fusible embedding materials customary to date, for example waxes, hydrogenated castor oil, plastics, such as cellulose ethers or esters or poly(meth)acrylic acid esters, the enveloping material according to the invention is used for this purpose. Customary pharmaceutical auxiliaries or additives furthermore can be co-used here, for example plasticizers, aroma substances, sweeteners, auxiliaries, such as, for example, talc, calcium carbonate, mannitol and cellulose powder, soluble dyestuffs and pigments.

The auxiliaries are added, if at all, to the enveloping mixture in amounts of, for example, 10 to 100% by weight, preferably 20 to 40% by weight, based on the weight of the cyclodextrins used.

Aroma substances, sweeteners and dyestuffs can be added to the mixtures in small amounts of, for example, 0.001% to 2%.

Further information on the customary auxiliaries and additives are to be found in the technical literature, for example the monograph by J.H. Saunders and K.C. Frisch "High Polymers", Verlag Interscience Publishers, 1962 and 1964.

The enveloping is advantageously carried out by spraying on solutions in organic solvents or suspensions or dispersions of the substances mentioned in organic solvents or water, it also being possible to add further auxiliaries, such as, for example, surface-active substances or pigments.

The spraying on is carried out, for example, in a coating kettle or in perforated kettles, or by the air suspension or fluidized bed process (for example Glatt fluidized bed unit WSG5).

The enveloping can also be carried out by the coacervation process in which so-called microcapsules or microparticles are formed.

The enveloping can also be carried out by coagulation of aqueous dispersions or suspensions above the minimum film formation temperature of the abovementioned substances by mixing the active compound with the dispersion and removing the water by drying.

Coated active compound particles and coated granules can be pressed to tablets and coated pellets can be inserted into hard gelatine capsules.

For coating active compound particles or granules which comprise active compound particles, more enveloping material is usually employed than in the case of pellets or tablets, since the surface which must be covered is considerably greater than in the case of pellets or tablets.

Since tablets as a rule are larger than pellets, the surface to be covered in the case of tablets is correspondingly smaller. For example, 0.02 to 1 part by weight of enveloping material can be used per part by weight of active compound or medicament formulation. A weight ratio of 1 part of active compound to 0.04 to 0.7, in particular 0.05 to 0.7, part by weight of enveloping

material is preferred, and 0.1 to 0.7 part by weight of enveloping material is especially preferred. Application of the enveloping material in solution, suspension or dispersion is expediently carried out at elevated temperature, preferably in a stream of air (intake air temperature 60 to 120°; temperature of the waste air up to 100°).

In the case of embedding processes, for example, 0.05 to 5.0 parts by weight of enveloping material, preferbly 0.08 to 3.0 parts by weight, especially preferably 0.1 to 2.0 parts by weight, are used par part by weight of active compound. These formulations are expediently prepared at temperatures between 10° and 100°.

The preparation of these presentation forms can be carried out, for example:

a) by dissolving or dispersing the active compounds or salts thereof in the enveloping material according to the invention or mixtures thereof, also with melting of the substances mentioned and subsequent recooling, comminution, possible addition of other substances, such as, for example, water-soluble or water-swellable substances, and pressing to tablets. Cooling of the melt and comminution can also be combined in one step by dispersing the melt in cold water or subjecting it to spray solidification.

Possible swelling substances are, for example: methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose (cellulose mixed ethers with propoxy, ethoxy and methoxy substituents), alginic acid and its salts (Na and Ca salt and also mixtures of sodium alginate and calcium salts, for example $CaHPO_4$), starch, carboxymethyl-starch, carboxymethylcellulose and salts thereof (for example the Na salt), gum arabic, karaya gum, ghatti gum, agar-agar, carrageen, xanthan gum, propylene glycol alginate, pectin and tragacanth.

b) By mixing the active compounds with the enveloping material according to the invention and if appropriate swelling substances or mixtures of these substances, also using heat, and, for example, pressing the mixtures, where appropriate after addition of further auxiliaries, to tablets or shaping to pellets and granules.

c) By mixing the active compounds with solutions of the enveloping material according to the invention in organic solvents, such as ethanol, ethyl acetate, acetone or isopropanol, if appropriate mixing with carrier materials, such as celluloses, and subsequent evaporation of the solvents and mixing of the embedded active compound obtained with further auxiliaries and processing to shaped articles, such as tablets, granules or pellets.

d) By moistening a mixture of the active compounds and of the enveloping material according to the invention, and, if appropriate, the swelling substances mentioned with organic solvents, such as ethanol, ethyl acetate, acetone or isopropanol, if appropriate with addition of binders, such as polyvinylpyrrolidone or copolymers of polyvinylpyrrolidone and polyvinyl acetate, granulation of the mixture obtained, subsequent drying, addition of any other auxiliaries and, for example, pressing of the mixture to tablets.

The preparation of these medicament formulations is carried out quite generally in a manner which is known per se, it being possible for the known and customary pharmaceutical auxiliaries and other customary excipients and diluents to be used in addition to the enveloping material according to the invention.

Possible excipients and diluents of this type are, for example, substances which are recommended or mentioned as auxiliaries for pharmacy, cosmetics and related fields in the following literature references:

Ullmanns Encyklopädie der technischen Chemie (Ullmanns Encyclopaedia of Industrial Chemistry), Volume 4 (1953), pages 1 to 39; Journal of Pharmaceutical Sciences, Volume 52 (1963), page 918 et seq., H.V. Czetsch-Lindenwald, Hilfsstoffe für Pharmazie und angrenzende Gebiete (Auxiliaries for Pharmacy and Related Fields); Pharm. Ind., Volume 2, 1961, page 82 et seq.; and Dr. H.P. Fiedler, Lexikon der Hiltsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete (Dictionary of Auxiliaries for Pharmacy, Cosmetics and Related Fields), 2nd Edition, Editio Cantor, Aulendorf in Württemberg (1981).

Examples of customary auxiliaries, excipients and diluents are gelatin, naturally occurring sugars, such as cane sugar or lactose, lecithin, pectin, starch (for example maize starch) and starch derivatives, galactomannans, polyvinylpyrrolidone, gelatin, gum arabic, alginic acid, tylose, talc, silicic acid (for example colloidal) or highly disperse SiO_2, laevulose, tragacanth, sodium chloride, stearates, magnesium salts and calcium salts of fatty acids having 12 to 22 C atoms, in particular the saturated acids (for example stearates), polyethylene glycol having an average molecular weight of between 200 and 20,000, preferably between 200 and 5000, in particular between 200 and 1000, or mixtures thereof, and/or polymers of vinylpyrrolidone and/or copolymers of vinylpyrrolidone and vinyl acetate, esters of aliphatic saturated or unsaturated fatty acids (2 to 22 C atoms, in particular 10 to 18 C atoms) with monohydric aliphatic alcohols (1 to 20 C atoms) or polyhydric alcohols, such as glycols, glycerol, diethylene glycol, pentaerythritol, sorbitol, mannitol and the like, which can optionally also be etherified, benzyl benzoate, dioxolanes, glycerol formals, tetrahydrofurfuryl alcohol, polyglycol ethers with C_1- to C_{12}-alcohols, dimethylacetamide, lactamides, lactates, ethyl carbonates, silicones (in particular medium-viscosity polydimethylsiloxanes), calcium carbonate, sodium carbonate, calcium phosphate, sodium phosphate, magnesium

carbonate, gum arabic, alginic acid, stearates, talc and substances having a similar action.

In addition, the presentation forms can comprise surface-active substances. Examples which may be mentioned are: alkali metal soaps, such as alkali metal salts of higher fatty acids (for example Na palmitate or Na stearate) or derivatives thereof (for example Na ricinoleate sulphuric acid ester); sulphurized compounds or sulphonated compounds which are formed by reaction of higher fatty alcohols with sulphuric acid or chlorosulphonic acid and are employed, for example, as sodium salts (for example sodium lauryl sulphate, sodium cetyl sulphate, sodium stearyl sulphate and sodium cetylsulphonate); salts of bile acids; saponins; quaternary ammonium compounds; partial fatty acid esters of sorbitan; partial fatty acid esters and fatty acid esters of polyoxyethylene sorbitan; sorbitol ethers of polyoxyethylene; fatty acid esters of polyoxyethylene; fatty alcohol ethers of polyoxyethylene; fatty acid esters of sucrose; fatty acid esters of polyglycerol; proteins; and lecithins.

The presentation forms can also comprise fillers, especially if compressed tablets are to be prepared. Possible fillers are:
purified cellulose or microcrystalline cellulose, calcium hydrogen phosphate, lactose, starches (for example potato starch, maize starch), glucose, mannitol and sucrose, and fillers having a binder function, such as microcrystalline cellulose, hydrolyzed or partly broken-down starches and mixed crystals of cellulose powder and lactose.

The presentation forms moreover can comprise flow regulators, such as, for example, highly disperse silicic acids. The use of mould release agents in the presentation form furthermore may be appropriate. Mould release agents which could be mentioned are: talc or siliconized talc, calcium stearate and magnesium stearate, stearic acid, paraffin, hydrogenated fats and oils and silicone oil emulsions. As a rule, however, it is not necessary to

add mould release agents, since the cyclodextrins themselves already have a mould release agent character.

Other possible auxiliaries are also substances which cause disintegration (disintegrating agents), such as crosslinked polyvinylpyrrolidone, sodium carboxymethyl-starch, sodium carboxymethylcellulose, formaldehyde-gelatin, formaldehyde-casein, polyacrylic acid and ultra-amylopectin.

The addition of stabilizers, dyestuffs, antioxidants and complexing agents (for example ethylenediaminotetraacetic acid) and of acids such as citric acid, tartaric acid, maleic acid and fumaric acid furthermore is possible.

Antioxidants which can be used are, for example, sodium metabisulphite, cysteine, ascorbic acid and esters thereof (for example palmitate), flavanoids, gallic acid alkyl esters, butylhydroxyanisole, nordihydroguajetic acid, tocopherols and tocopherols + synergists (substances which bond heavy metals by complexing, for example lecithin, ascorbic acid, citric acid and phosphoric acid).

Examples of possible preservatives are sorbic acid, p-hydroxybenzoic acid esters (for example lower alkyl esters), benzoic acid, sodium benzoate, trichloroisobutyl alcohol, phenol, cresol, benzethonium chloride and formalin derivatives.

Solvents from the group comprising aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated hydrocarbons, cycloaliphatic, heterocyclic solvents and mixtures thereof can be used for application of the enveloping material according to the invention. Typical solvents are, inter alia, acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylglycol monoethyl ether, ethylene glycol monoethyl acetate, dichloromethane, 1,2-dichloroethane, 1,2- or 1,3-dichloropropane, carbon tetrachloride, nitroethane, nitropropane,

tetrachloroethane, cyclohexane, cyclooctane, benzene, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diethylene glycol dimethyl ether, water and mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethanol, methylene chloride and methanol, and 1,2-dichloroethane and methanol. These solvents are removed again in the course of the enveloping process.

Possible active compounds which can be formulated with the enveloping material according to the invention are those which can be administered orally and for which it may be desirable that they are released only in the colon. These include, for example, intestinal agents, such as mesalazine (5-aminosalicylic acid) or laxatives, such as bisacodyl, and furthermore peptides, cardiovascular therapeutics, antirheumatics/analgesics, agents for the treatment of diseases of the large intestine (Crohn's disease, colitis ulcerosa), antiasthmatics, antifibrinolytics, antihaemorrhagics, antitumour agents, enzyme preparations, antibiotics, antimycotics and substances having an action on the CNS (central nervous system).

An important class of active compounds which are to be released only in the colon are those having a peptide or protein structure, for example insulin. They would be broken down by the endogenous proteolytic enzymes in the upper sections of the intestine before they can have an action; in contrast, the content of proteolytic enzymes in the colon is so low that an adequate action and absorption time remains.

Examples of peptide active compounds are, in particular: ACTH (adrenocorticotropic hormone), corticostatin, calcitonin, insulin, oxytocin, somatostatin and analogues, LHRH analogues, bombesin analogues, cholecystokinin and derivatives, endothelin and analogues, thrombin inhibitors, peptide growth factors (for example IGF, EGF, NGF), magainins (PGS peptides), gastric analogues, parathormone analogues, neurokinin and analogues, VIP (vasoactive intestinal polypeptides) and analogues, ANP (atrial natriuretic peptide) and

analogues, neokyotrophin and analogues, angiotensin analogues, encephalins, dynorphins, dermorphins, deltorphins, renin-inhibiting peptides, tumour growth factor peptides, MSH (melanocyte stimulating hormone) analogues, mitotoxins, tyrphostins, chromogranin A, thymopentin, TRH (thyrotropin releasing hormone) and analogues, substance P, tuftsin, fibronectin and peptidic immunomodulators, such as cyclosporin A, FK 506 and neuropeptide Y.

The enveloping material according to the invention is virtually impermeable in simulated small intestine juice. After incubation in the "colonic microflora test" ("CMT"; compare dissertation by C. Wohlschlegel, Freiburg, 1990), on the other hand, enzymatic breakdown of CD takes place, through which the films become porous and therefore permeable, so that the enveloped active compounds can be released and can act in the colon.

A particular advantage of the new enveloping material lies in the fact that its constituents are known and are completely physiologically acceptable.

All the percentage data above and below are percentages by weight. Temperatures are stated in °C.

Example 1: Enveloping material (film)

1.1 Preparation

A mixture of 4 g of DEP and a dispersion of 4 g of CD in 27.3 ml of water is added to 66.6 g of a 30% aqueous dispersion (commercial preparation) of a copolymer of 30 parts of ethyl acrylate, 65 parts of methyl methacrylate and 5 parts of trimethylammonioethyl methacrylate chloride in the course of 2 minutes, while stirring (180 revolutions per minute), and the mixture is stirred at this temperature for a further 10 minutes.

For characterization of the film, a film is drawn from the dispersion thus obtained on polyester films using the Erichsen film-drawing apparatus model 509/1 at 40° and at a drawing rate of 12 mm/second. A doctor blade having a slit height of 200 µm is used. Film formation takes about 30 minutes, and the film is then kept on the

polyester film at 20-25° and detached from the carrier film again for actual characterization.

Dispersions of the following compositions are obtained analogously (in %):

No.	Film-forming agent	Plasticizer TEC	Plasticizer DEP	CD	Water
1	19.23	3.85	0	3.85	73.07
2	19.23	3.85	0	5.77	71.15
3	19.23	3.85	0	7.69	69.23
4	19.23	0	3.85	3.85	73.07
5	19.23	0	3.85	5.77	71.15
6	19.23	0	3.85	7.69	69.23
7	19.23	0	3.85	9.62	67.30
8	17.24	0	3.45	10.34	68.97
9	16.95	0	3.39	11.86	67.80
10	16.66	0	3.33	13.33	66.68
11	16.39	0	3.28	14.75	65.58
12	16.13	0	3.23	16.13	64.51
13	15.63	0	3.13	18.75	62.49

1.2 Film characterization

1.2.1 Film thickness determination

The film thickness is determined by a magneto-inductive method (Minitest 3000, Erichsen). Measurements are taken at six different points and the average of the results is obtained. The film thicknesses are between 35 and 70 µm.

1.2.2 Permeability in simulated small intestine juice

The films are investigated in respect of their permeability with the aid of Franz cells (compare C.L. Gummer et al., Int. J. Pharm. 40 (1987) 101-104). For this, a piece of film is clamped between the donor and acceptor. The acceptor vessel is filled with simulated small intestine juice (phosphate buffer pH 6.8 R, DAB 10) and kept at a controlled temperature of 37°C. The liquid is mixed thoroughly with a magnetic stirrer. The donor contains a concentrated solution of mesalazine (5 µg/ml) in phosphate buffer pH 6.8. The medicament serves as an indicator substance for the permeability of the film. After 2 hours, 4 hours and 6 hours, a sample of 2 ml is taken from the acceptor and is replaced by phosphate buffer. The sample is measured photometrically (Uvikon 820, wavelength 330 nm), the detection limit being 2 µg/ml. The permeability of the films is determined with the aid of the mesalazine concentration determined in the acceptor. All the films mentioned in section 1.1 were practically impermeable for up to 6 hours under these conditions.

1.2.3 Degradability in the CMT (colonic microflora test)

The CMT (compare Pharm. Pharmacol. Lett. (1992) 2, 62-65) is used to check the degradability in the large intestine. This is a mixture of pig caecum, excretory secretion from ileostomy patients and phosphate buffer pH 6.4 R, DAB 10 (5:5:1). The mixture is incubated under anaerobic conditions, that is to say under N_2/CO_2 gassing in a ratio of 5:1, at 37°.

Circular pieces of film having a radius of about 0.7 cm are incubated with the ileostomy/pig caecum mixture for defined periods of time (between 2 and 6 hours) and are then rinsed with water and dried at room temperature. To prepare the samples, the pieces of film are then stuck onto a microscope slide and vapour-deposited with gold. The surface of the films is examined by scanning electron microscopy. A significantly porous structure is found, in contrast to samples of film which

have not been treated with CMT.

Example 2: Enveloping material (film)

A mixture of 1.2 g of DEP and a dispersion of 4.75 g of CD in 36.3 g of water is added to 50 g of a 25 % aqueous dispersion (commercial preparation) of ethyl cellulose in the course of two minutes while stirring (180 revolutions per minute), and the mixture is stirred at room temperature for a further 15 minutes.

Analogously, dispersions of the following compositions are obtained (in %):

No.	Film forming agent	Plasticizer			CD	Water
		TEC	DEP	DBS*)		
1	11.93	1.45	0	0	3.44	83.18
2	10.70	1.30	0	0	5.15	82.85
3	11.93	0	1.45	0	3.44	83.18
4.	10.70	0	1.30	0	5.15	82.85
5	11.93	0	0	1.45	3.44	83.18
6	10.70	0	0	1.30	5.15	82.85

DBS = dibutyl sebacate

Example 3: Coated tablets

3.1 Preparation

330 g of the commercial preparation according to Example 1.1 are mixed with a suspension of 20 g of TEC and 30 g of CD in 370 ml water by stirring with a blade stirrer, and the mixture is further stirred for another 10 minutes.

1.5 kg of tablet cores of the following composition are sprayed with the aid of this dispersion:

Mesalazine	100 mg
Microcrystalline cellulose	35 mg
Lactose	35 mg
Polyvinylpyrrolidone	7 mg
Maize starch	20 mg
Highly disperse silicic acid	1.6 mg
Carboxymethylcellulose, Na salt	1.8 mg
Magnesium stearate	1.8 mg
	204.2 mg

(Diameter 8 mm; height 3.76 mm; surface area 1.96 cm^2)

The dispersion is stirred with a blade stirrer during the spraying operation (continuous spraying procedure, spraying air 3 bar; flow rate 10 g × $minute^{-1}$; nozzle diameter 0.6 mm; temperature: entry 63°, core bed 33°, exit 44°; spraying duration about 1 hour). The resulting tablets coated with in each case 17.6 mg of enveloping material (individual weight 221.8 mg) are dried overnight at 40°.

3.2 Characterization of the tablets

3.2.1 Stability in the artificial colon.

In order to test the stability of the tablets in the artifical colon, they are moved in the degradation tester for 6 hours and subsequently investigated optically. Furthermore, the concentration of mesalazin in the test medium ist determined. Under these conditions, all tablets were stable for at least 6 hours.

3.2.2 Degradability in the CMT

The tablets are incubated in the CMT for 4,6 and 24 hours. Subsequently, their liberating characteristics are determined in a paddle apparature. It is found that the permeability of the tablets increases with a higher content of CD and longer incubation time.

Example 4: Coated Tablets

According to Example 2, 500 g of the commercial dispersion of ethyl cellulose is mixed with a suspension of 12 g of TEC and 47.5 g of CD in 670.5 ml of water by stirring with a blade stirrer. The mixture is stirred for another 10 minutes, and then the procedure described in Example 3 is followed.

The Claims defining the invention are as follows:

1. Oral medicament form comprising at least one active compound and at least one enveloping material which surrounds the active compound and comprises at least one film-forming agent which is insoluble in water and the digestive juices, characterized in that the enveloping material additionally comprises at least one cyclodextrin and/or at least one of its derivatives.

2. Enveloping material for oral medicament forms, comprising at least one film-forming agent which is insoluble in water and the digestive juices, characterized in that it additionally comprises at least one cyclodextrin and/or at least one of its derivatives.

DATED this 20th day of October 1993,

MERCK PATENT GESELLSCHAFT
MIT BESCHRANKTER HAFTUNG
By Its Patent Attorney
DAVIES COLLISON CAVE

Abstract

The invention relates to an oral medicament form comprising at least one active compound and at least one enveloping material which surrounds the active compound and comprises at least one film-forming agent which is insoluble in water and the digestive juices, characterized in that the enveloping material additionally comprises at least one cyclodextrin and/or at least one of its derivatives.